Grant #623BR-2
#623BR-1
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Act: 2/1/71
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PHARMACOLOGY

Comm.
Dr. Andervont
Dr. Cattell
Dr. Meier

THE COUNCIL FOR TOBACCO RESEARCH–U.S.A., INC.
110 EAST 59TH STREET
NEW YORK, N. Y. 10022
(212) 421-8885

Application For Renewal of Research Grant
(Use extra pages as needed)

First Renewal ☑ Second Renewal ☒ Date: Jan. 9, 1973

1. Principal Investigator (give title and degrees):

Walter B. Essman, M.D., Ph.D., Professor

2. Institution & address:

Queens College of the City University of New York
65-30 Kissena Boulevard
Flushing, New York 11367

AND

Research Foundation of the City University of New York
1411 Broadway
New York, New York 10018

3. Department(s) where research will be done or collaboration provided:

Departments of Psychology and Biochemistry
Queens College of the City University of New York

4. Short title of study:

Studies of Nicotine Action Upon Memory Consolidation

5. Proposed renewal date: April 1, 1973

6. How results to date have changed earlier specific research aims:

Those results obtained to data have not changed earlier specific research aims.

7. How results to date have changed earlier working hypothesis:

There have been no essential changes in earlier working hypotheses.

8. Any additional facilities now required? Describe briefly:

No additional facilities are required.

9. Any changes in personnel? Append biographical sketches of new key professional personnel:

No personnel changes are indicated and no additional professional personnel additions are contemplated.

10. Append outline of experimental protocol for ensuing year. See attached protocol.

11. List publications or papers in press resulting from this or closely related work. (append reprints or manuscripts not previously sent).

Alterations in the behavioral and biochemical effects of electroconvulsive shock with nicotine. Psychon. Sci., 1968, 12, 107-108 (with M.I. Steinberg and M.I. Golod).

Alterations in brain serotonin metabolism mediating enhanced memory consolidation. In: Cerletti, A., & Bove, F.J. (Eds.) The Present Status of Psychotropic Drugs. Amsterdam: Excerpta Medica, 1969, Pp. 305-306.

Central nervous system metabolism, drug effects, and higher functions. In: Smith, W.L. (Ed.) Drugs and Cerebral Function. Springfield: Chas. Thomas, 1970, Pp. 151-175.

The role of biogenic amines in memory consolidation. In: Adám, G. (Ed.) The Biology of Memory. Budapest: Akademiai Kiado Publ., 1970, Pp. 213-238.

Metabolic and behavioral consequences of nicotine. In: Smith, W.L. (Ed.) Cerebral Function Development and Drug Action. Springfield, Ill., Chas. Thomas, 1972, Pp. 273-287.

(publications continued on attached sheet)

12. Summary progress report (append in standard form as separate document, unless recently submitted).

Drugs affecting facilitation of learning and memory. In: Rubin, A.L. (Ed.) Search for New Drugs. N.Y.: Dekker, 1972.

Drug effects and learning and memory processes. In: Garattini, S., and Shore, P. (Eds.) Advances in Pharmacology and Chemotherapy. N.Y.: Academic Press, 1971b, Pp. 241-330.

Cholinergic mechanisms and avoidance behavior acquisition: effects of nicotine in mice. Psychol. Rep., 1971, 29, 987-993 (with S.G. Essman).

Changes in cholinergic activity and avoidance behavior by nicotine in differentially housed mice. Int. J. Neurosci., 1971, 2, 199-206.

Nicotine-related neurochemical changes: some implications for motivational mechanisms and differences. In: Dunn, W.J., Jr. (Ed.) Motivation in Cigarette Smoking, 1972 (In Press).

Neurochemical modulation of experimentally induced retrograde amnesia. Confinia Neurol., 1973 (In Press).

Age dependent effects of 5-hydroxytryptamine upon memory consolidation and protein synthesis. Physiol. Behav., 1973 (In Press).

Effects of ECS and intracranial 5-HT on cerebral protein synthesis. Paper presented at Fourth Annual Winter Conference on Brain Research, Vale, Colorado, Jan. 1972 (with E. Heldman).

13. Budget for the coming year:

A. Salaries (give names or state "to be recruited")	% time	Amount
Professional (give % time of investigator(s) even if no salary requested)		
Technical		
Technical Assistant (to be selected)	100%	8,500.00
Grant Technician (Sheryl Sherman)	50%	4,340.00
Fringe Benefits		2,054.00
	Sub-Total for A	14,894.00
B. Consumable supplies (by major categories)		
Animal Purchases		1,100.00
Animal food, bedding, and cleaning supplies		600.00
Chemical and glassware		770.00
Disposable cages		300.00
	Sub-Total for B	2,770.00
C. Other expenses (itemize)		
Travel: International Symposium on Serotonin, Sassari, Sardinia, May, 1973 Federation of Societies for Experimental Biology, Atlantic City, New Jersey, April, 1973 Winter Conference on Brain Research, Vale, Colorado, Jan., 1974	Sub-Total for C	1,100.00
	Running Total of A + B + C	18,764.00
D. Permanent equipment (itemize)		
None		
	Sub-Total for D	
E. Indirect costs (15% of A+B+C)	E	2,815.00
	Total request	21,579.00

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14. Other sources of financial support:
List financial support from all sources, including own institution, for this and related research projects.

CURRENTLY ACTIVE

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates
Metabolic Responses to Stress-Tobacco Smoke Interactions	C.T.R.	$40,000.00	10/1/72 - 9/30/73

PENDING OR PLANNED

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates

It is understood that the investigator and institutional officers in applying for a grant have read and accept the Council's "Statement of Policy Containing Conditions and Terms Under Which Project Grants Are Made."

Checks payable to
Research Foundation of C.U.N.Y.

Mailing address for check:
1411 Broadway
New York, New York 10018

Principal investigator
Typed Name Walter B. Essman
Signature Walter B Essman Date 1/10/73
Telephone 212 762-5949
Area Code Number Extension

Responsible officer of institution
Typed Name Nathaniel H. Siegel - Vice President
Title Hannah Petzenbaum - Research Foundation Queens College
Signature [illegible] Date
Telephone
Area Code Number Extension

10035394O3

10. Brief Description of Objectives or Specific Aims:

The overall goal of this project is to relate several of the effects of nicotine treatment in experimental animals to the process of memory consolidation. This relationship will be explored in several experiments designed to study the metabolic effects of nicotine treatment under several conditions, and to relate these effects to behavioral paradigms, within which memory consolidation can be objectively defined. Previous results have substantially supported the hypothesis that the administration of nicotine sulfate, at critical times prior to training for acquisition of a conditioned response can, under appropriate conditions, facilitate memory consolidation through the attenuation of an experimentally-induced amnesia effected by post-conditioning electroconvulsive shock.

The time course of nicotine effects in relation to both memory consolidation and central metabolic events, which parallel experimentally-induced disruption of such consolidation, has been defined in prior studies, and several metabolites of nicotine have been specified as possibly accounting for the facilitation of memory consolidation. The interaction between nicotine metabolites and the amnesic event, electroconvulsive shock, has been considered in a series of studies which have indicated that the regional metabolism of serotonin (5-hydroxytryptamine) in the brain can be altered by nicotine, its metabolites, and the interaction of these with the amnesic properties of post-conditioning electroconvulsive shock.

The major objective of continued investigation of nicotine action and the memory consolidation process concerns four specific areas wherein this relationship will be intensively investigated; these areas of further investigation represent those which have previously been outlined for the full three years of grant support request, for which the first year was approved and is currently active.

The two aspects of the initially proposed areas that have been extensively explored within the currently active grant period bear upon the relationship between nicotine and its metabolites to the amnesic properties of post-conditioning agents or events as a means of assessing parameters relevant to the memory consolidation process. Further exploration will concern: (1) the effects of nicotine and several of its active metabolites upon memory consolidation as a function of development; (2) identification of the regional uptake and distribution of nicotine metabolites in the brain following administration, and thereby to relate uptake and distribution to cellular and subcellular effects; (3)the temporal relationship between central uptake and distribution and alterations in cerebral amine and metabolism; and (4) specific cellular effects of nicotine and its metabolites as these effects relate to the memory consolidation process and its disruption by specific amnesic agents or events.

Progress in the current area of investigation has been summarized in the appended reports and specifically detailed in the included reprints and preprints of published papers. These areas of completed work and work in progress have concerned the effects of chronic administration of nicotine in mice where such effects have been behaviorally evaluated utilizing both post-and-active avoidance conditioning procedures whereas the retention of passive avoidance behavior as currently facilitated through such chronic treatment, the retention of active avoidance behavior appears to be selectively impaired by such chronic treatment, depending upon endogenous conditions conferred on the basis of differential housing. This line of investigation has yielded an extremely useful model for memory retardation in avoidance conditioning, where such memory pathology can be appreciably attenuated through the chronic administration of nicotine. A wide aspect of the proposed work which, again has seen considerable pro-

gress made, concerns the cellular effects of nicotine, particularly as these are concerned with cholinergic transmission at the synapse. Extension studies utilizing subcellular fractionation techniques have indicated that in specific regions of the mouse cerebral cortex, the acetylcholine content of synaptic vesicles represent thirty per cent of the bound acetylcholine in cerebral cortex; this contrasts with eleven per cent vesicular acetylcholine in the cerebral cortex of control animals. Furthermore, a time course study relating cholinergic changes to the amnesic effect of post-training electroconvulsive shock indicated that the optimal intervals for ECS induced amnesia, there was a twenty per cent decrement in vesicular acetylcholine levels. This observation again contrasts with the finding that animals treated with nicotine and then given electroconvulsive shock showed a sixty-four per cent increase in vesicular acetylcholine content. These findings, similar to previous observations concerned with serotonogenic changes brought about by nicotine and its metabolites, point to important basic cellular effects which underly basic mechanisms for those cognitive processes affected by nicotine. A further aspect of the cellular specificity of those effects brought about by nicotine and its metabolites has also been in progress over the past year and continues to yield results. These studies have utilized cellular separation techniques which allow a distinction to be made between a neuron-enriched and a flia-enriched fractionation from several representative areas of the mouse brain. Cellular effects of nicotine and several of its metabolites have been studied within this context insofar as time course, regional specificity of effect, and the nature of the changes in biogenic amines asfar as their cellular specificity.

It is anticipated that this work which will include data based on study-state kinetic estimates of cellular timeover for biogenic amines will be completed within approximately eight months and will therefore constitute an important basic step upon which further studies may then be elaborated.

7. Brief Statement of Working Hypothesis:

The administration of nicotine and several of its centrally active metabolites can, within the appropriate temporal and dosage parameters, alter the time course and efficacy of the memory consolidation process through effects initiated by cellular and regional alterations in brain amine metabolism. The process of memory consolidation, as facilitated by nicotine treatment (chronic, post-trial, or as a function of age), will be modified through alterations in centrally active biogenic amines, which may underlie the basic of experimentally induced retrograde amnesia,and through such modifications, a reduction in amnesia may be viewed as facilitation of memory consolidation.

8. Details of Experimental Design and Procedures:

The behavioral portion of all the experiments to be carried out will employ the single trial conditioning procedure, previously described in our protocols for establishing a stable avoidance response in one trial. This response, which is stable over time as well as within experimental conditions, has been successfully utilized to assess the amensia effect of electroconvulsive shock and other agents or events which, when presented in close temporal proximity with the acquisition trial experience, result in a reduction in the incidence of retention, as measured 24 hours later; amnesia and/or retention are assessed by measures of response latency so that criterion avoidance is defined on the basis of latencies in excess of five standard deviations of the mean latency exhibited on the training trial and an absence of retention, or retrograde amnesia, is defined as a response latency on the testing trial that is equivalent to or within one standard deviation of the mean response latency shown on the training trial. This procedure has been successfully utilized in our laboratory with over 20,000 mice during the nine to ten years within which the technique was originally devised by this investigation. A more detailed description of procedure, parameters covering acquisition and

retention, and some of the applications thereof, may be found in several publications (Essman & Alpern, 1965; Essman, 1968; Essman and Essman, 1969).

Animals utilized in all of the proposed studies will be CF-1 strain mice, (Mus Musculus), to be obtained from a commercial vendor (Carworth Farms, Inc., New City, New York), at weaning (21 days) and following adaptation to conditions of laboratory use (10/cage), will be utilized as experimental subjects at approximately 30 days of age or, in the case of the developmental studies proposed, animals will be bred in the laboratory specifically for purposes of obtaining precise age controls. The specific experiments to be conducted within the time specified for the proposed research will concern:

(1) the effects of nicotine and its active metabolites upon memory consolidation during early development;

(2) identification of the regional uptake and distribution of nicotine metabolites in the brain following administration;

(3) the temporal relationship between central uptake of nicotine and its metabolites and the distribution and alterations in biogenic amines;

(3) specific cellular effects of nicotine and its metabolites as related to memory consolidation;

9. Physical Facilities Available:

Two large air-conditioned laboratories and adjoining animal housing facilities ara available and currently in use by the investigator; the laboratories are completely equipped with all equipent necessary for the biochemical procedures required, with the exception of those equipment items requested in the budget. Additional studies will be concerned with the functional role of differential housing as a model for the induction of deficits in memory consolidation and the degree to which both acute and chronic administration of nicotine can alter these deficits. More specific, these experiments will concern a comparison of memory consolidation upon mice housed either in isolation or in groups following weaning

for various durations, the duration governing the apparent extent to which the memory consolidation deficit is in evidence. Studies in this are will therefore be directed toward evaluation of:

(a) Effects of acute pre-training nicotine administration;

(b) Effect of chronic pre-training nicotine administration;

(c) Interaction of acute pre-training nicotine treatment with electroconvulsive shock as an amesic agent;

(d) Interaction with post-training, post-ECS acute nicotine administration;

(e) Effects of pre-training intracranial nicotine administration;

(f) Effects of post-training intracranial nicotine administration;

In all cases the experiments proposed within this area of the investigation are employing the differentially housed mice indicated, with differring durations of isolation governing the degree to which the memory consolidation deficit occurs.

In the first series of experiments, the effects of chronic nicotine and its metabolites will be investigated in order to assess and compare chronicity of treatment with results already obtained on acute administration. Mice, beginning at approximately 30 days of age, will be given single daily injections of nicotine sulfate within a dose range of 0.25 mg/kg to 2.00 mg/kg, i.p. An equivalent volume of 0.9% saline will be given control animals. Compared with a single acute administration over the dose range indicated, animals will be given injections for 3 days, 7 days, and 21 days, with a single training trial given one hour following the final chronic administration. For each of these conditions, asingle post-training electroconvulsive shock will be given either immediately, 10 minutes, 20 minutes, or 60 minutes following the training trial. A testing trial will be given 24 hours following training, and the incidence of conditioned response retention will be measured. Data emerging from these experiments will allow for statements

regarding the temporal gradient foe ECS-induced retrograde amnesia as a function of both nicotine sulfate dosage and the duration of nicotine sulfate treatment at a given dosage prior to training. Inasmuch as preliminary data has clearly indicated that the temporal gradient for ECS-induced retrograde amnesia falls within one hour, the proposed intervals for post-training ECS will allow for statements regarding either a contraction of the temporal gradient (i.e. , a reduction of the post-training time interval within ECS results in retrograde amnesia), or an expansion of the gradient (i.e., an extension of the time following training, within which ECS will produce a retrograde amnesia). Since previous data have clearly indicated that the temporal gradient for retrograde amnesia is appreciably shortened as a redult of pretreatment with a single dose of nicotine sulfate, the extent to which, within the present study, these alterations hold as a result of chronic treatment, will be determined. Paralleling the present study, groups of animals, given nicotine sulfate, followed by acquisition training with sham-ECS, will serve as both controls for the effect of ECS as well as provide a baseline from which the effects of chronic nicotine treatment upon acquisition of the conditioned response may be assessed.

Once the conditions under which appropriate dosage and effects of prolonged nicotine treatment are determined as an outcome of the present experiments, the selected group of related compounds and metabolites of nicotine will be utilized in similar chronic studies. These will include nornicotine, (-) cotinine, 3, pyridylacetic acid, myosmine, and anabasine, and will be given under the same conditions of chronic treatment in doses ranging from 0.10 mg/kg to 0.50 mg/kg.

Training, ECS, and sham-ECS treatment and post-training retention trials, as described for the previous experiments, will be given, and the degree to which the temporal gradient for retrograde amnesia is affected by these compounds will

be assessed in a manner similar to that described above. These experiments should provide data which will allow for statements regarding the effects of chronic nicotine and metabolite treatment upon memory consolidation. The experimental literature contains virtually no studies regarding the behavioral effects of chronic nicotine treatment, and any behavioral toxicity associated with chronicity may be determined from these studies; more specifically, should such findings emerge, these may then be more clearly identified with one of the specific metabolites.

The effects of post-conditioning drug treatment upon memory consolidation has been explored by several investigators with somewhat controversial and discrepancy results emerging. The general premise underlying such studies is that the process of memory consolidation, which is usually initiated by a learning experience, lasts for a period of time following such an experience, within which the process may possibly be enhanced by appropriate drug treatment. If this interval has superimposed upon it a disruptive agent, such as electroshock, a high incidence of retrograde amnesia for the experience results. If the training-ECS sequence is followed by central changes, associated with drug treatment, the disruptive effect of ECS and, possibly, the rate of consolidation might be expected to be altered, providing that the parameters for such a sequence are appropriate. The major purposes of the second series of experiments will be to investigate the results of administered effective doses of nicotine (1 mg/kg) and its metabolites (0.25 mg/kg) upon the amnesic effect of electroshock, where such treatment is given following ECS. The training-ECS interval will be adjusted to coincide with those post-training times within which, based upon previous data, ECS is effective in producing retrograde amnesia. Nicotine sulfate and the above-named metabolites will be given either immediately, 1 minute, 5 minutes, or 10 minutes following ECS administration,

and a testing trial to measure the incidence of retrograde amnesia and/or conditioned response retention will be given 24 hours following training.

The critical parameters in this series of studies, therefore will be: (a) the training-ECS-drug treatment interval, and (b) the interaction of these intervals with the training-ECS interval. Control groups, receiving physiological saline, paralleling the above described conditions, and drug-treated controls, given sham-ECS, will be utilized to evaluate the significance of emerging results.

The major point toward which this series of experiments is directed is whether the memory consolidation interval is sufficiently labile to permit the interposition of any post-amnesic treatment nicotine effects.

A further series of experiments will concern the relationship between nicotine and several of its active metabolites upon the memory consolidation process as a function of development. Previous data, summarized in the supporting data section of this application, have indicated that the CF-1 strain mouse, at 17 days of age, is highly resistant to the amnesic effect of electroconvulsive shock, as compared with younger or older mice of the same strain, and that mice at 15 and 16 days of age show a reduced incidence of ECS-induced retrograde amnesia, as compared to mice of 20 days, or more, of age. A developmental parllel to these behavioral findings appears to reside in levels of 5-hydroxytryptamine and 5-hydroxyindoleacetic acid, and also in the turnover of the former in the brain.

Conditions which maximize resistance to retrograde amnesia, induced by ECS, appear to be developmentally dependent, and it is within this context that the effects of nicotine and several of its metabolites will be investigated. The basic hypothesis underlying this series of studies is that the facilitation of memory consolidation by nicotine and its active metabolites will be age-dependent insofar as age-dependent differences in memory consolidation are present. It would therefore seem reasonable to assume that nicotine and its active metabolites will be

more effective in altering memory consolidation at those ages where the amnesic effect of electroshock is maximal. Groups of mice, ranging in age from 15 to 30 days, will be treated with either nicotine sulfate (1.0 mg/kg) or one of its active metabolites (0.25 mg/kg) 45 to 60 minutes prior to the administration of a single training trial, as previously described, followed at intervals of either 0, 10, 20, or 60 minutes by a single transcorneal ECS. A testing trial, given 24 hours following training, will assess the extent to which drug treatment was effective in attenuating or antagonizing the amnesic effect of electroshock.

Control groups, given physiological saline under each of the experimental conditions specified, and drug-treated animals, given sham-ECS, will be utilized as controls. The differential alterations in brain 5-hydroxytryptamine level and metabolism during early development represents an ideal system within which nicotine and its metabolites, as agents which, in themselves, alter relatively stable levels of 5-HT metabolism, may be investigated. Within this context, there resides the important question as to whether nicotine and its metabolites, in producing predictable alterations in amine metabolism, will do so reversibly during early development, or whether these effects during early development result in changes, the magnitude or duration of which may be considerably discrepant from that observed in the adult animal. For these reasons, it will be a further purpose of this investigation to study the changes produced by nicotine and its active metabolites upon brain 5-HT levels and metabolism during early development. These procedures will essentially parallel the behavioral portion of the study, as outlined above, and will follow through the use of techniques previously described.

Through the use of spectrofluorometric procedures, developed in this laboratory, it should be possible to characterize nicotine and its active metabolites and, based upon such characterization, to identify regional locus following systemic

injection. These procedures will basically involve a series of experiments in which, at several times following the systemic injection of nicotine sulfate or active metabolites, mentioned above, mice will be sacrified by cervical dislocation, the whole brain will be removed, transferred immediately to freon, chilled in a jacked of liquid nitrogen, and upon rewarming to -30° C, macrodissection will be carried out for isolation of several areas of the brain, to include: olfactory bulbs, cerebral cortex, mesencephalon, diencephalon, limbic system structures, hypothalamus, and cerebellum. From each of these areas spectrofluorometric determination of previously standardized procedures for estimation of nicotine and its metabolites will be carried out and, in addition, the distribution of centrally active biogenic amines will be concommitantly determined from the same regions. These studies will allow for statements to be made regarding (a) the regional uptake and distribution into the central nervous system of nicotine and its metabolites following central administration, (b) the temporal relationship between dosage and central uptake, and (c) the temporal relationship between central utake, distribution, and changes in the metabolism of biogenic amines. In addition to obtaining data concerned with serotonin, which is the basis of the theoretical model within which nicotine effects and memory consolidation are being investigated in the present studies and those proposed, the availability of regionally specific tissue from mouse brain in the proposed studies also allows for determination of acetylcholine levels and acetylcholinesterase activity. In the latter regard, there has been no published information on the relationship between nicotine uptake and its metabolite distribution in the central nervous system, and cholinergic changes which relate temporally to these conditions.

A final aspect of the proposed work relates to the cellular effects of nicotine

and its metabolites, as these are related to memory consolidation. This issue is given preliminary support in this application by methodological and empirical findings from our laboratory, which suggest the feasibility of obtaining reasonably purified neuronal and glial fractions from mouse brain and demostrating that in vivo treatment, resulting in retrograde amnesia in mice, exerts a differential effect at the cellular level; i.e., neurons are affected over a differentiate time course than glia following ECS, and the effect in glia is more prolonged than that in neurons. The specific effect to which these findings are in alterations in 5-hydroxyindoleacetic acid following electroconvulsive shock. Through the utilization of the fractionation technique, which involves a discontinuous sucrose-ficoll density gradient centrifugation, a neuronal and glial pool can be separated from myelin and red cells. These fractions have been morphologically verified in both phase-contrast and electron microscopy and their purity has been verified by the relative rations of acetylcholinesterase in the respective fractions. The purpose of this final series of experiments will be to assess the effect of nicotine and its metabolites on cellular levels of biogenic amines, and study the interaction of drug treatment with electrcconvulsive shock upon these cellular levels. Specifically, we may anticipate that cellular changes, which parallel retrograde amnesia produced by ECS, will be blocked, attenuated, or antagonized by nicotine or its active metabolites under these conditions where these behaviorally modify the amensic effect of elctroshock. All of the experimental conditions will be applied in vivo, following which the brains will be removed, prepared, and extracted, as previously described, with the addition of the fractionation procedure for isolation of neuronal and glial pools in several of the areas described. These studies should allow for a considerable degree of useful data to emerge regarding differences in the regional cellular response in the central nervous system to nicotine and its meta-

bolites. It should be noted that this question has not, in any case, been treated in any of the experimental literature and costitutes what is probably an exceedingly important issue insofar as the central effects of nicotine are concerned.

The additional studies that have been proposed concern (Table 7) the application of a differential housing model for the evaluation of facilitative as well as potentially disruptive effects of nicotine treatment upon memory consolidation can be governed by the duration of isolation housing under which animals post weaning are maintained. The six experimental aspects of this investigation have been outlined in an earlier part of the application and the biochemical assessment of nicotine induced changes are paralleled those procedures previously described.

Should additional results warrant further investigation of cholinergic mechanisms relating either to retrograde amnesia or the interaction of this phenomenon with nicotine treatment, additional studies will be initiated, utilizing subcellular fractionating techniques to evaluate the description of cholinergic effects mediated at the nerve ending which offer implications for the role synaptic processes in nicotine mediated changes in memory consolidation.